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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/711,272	11/09/2000	Timothy Norris	62814-A/JPW/GJG	6700

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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	PAPER NUMBER
1624	9

DATE MAILED: 08/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/711,272	NORRIS ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,14-32,50 and 52-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *61* is/are allowed.

6)☒ Claim(s) *1-7,14-32,50,52-60 and 62-68* is/are rejected.

7)☒ Claim(s) *69-72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 6/19/02. Applicants have amended claims 5, 14, 23, and 50. Claims 55-72 are new. There are forty-eight claims pending and under consideration. Claims 1-4 are compound claims. Claims 5-7, 55-60, and 62 are composition claims. Claims 14-23, 50, and 63-72 are use claims. Claims 24-32, 52-54, and 61 are method of making claims. This is the second action on the merits. The application concerns a specific crystal form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, which has Chemical Abstracts registry number 183319-69-9.

Response to Amendment

2. Applicants' addition of a carrier to composition claim 5 overcomes the indefiniteness rejection made in point #5. Applicants replaced "a hyperproliferative disorder" with "abnormal cell growth" in claim 14 and point the paragraph spanning pages 23 to 24 as indicating what they intend. Thus, the indefiniteness rejection made in point #6 is withdrawn.. Applicants point to the phase II studies in the passage spanning line 19, page 51 to line 35, page 52 as enabling their claims to treating specific cancers. This is persuasive, and the enablement rejection to claim 16 is withdrawn. Claim 50 is an independent claim, not limited to the polymorph of claim 1. In lines 9-10, column 14 of Schnur ('498) treatment of hepatic carcinoma with N-(3-ethynylphenyl)-6,7-bis(2-

methoxyethoxy)-4-quinazolinamine in taught. Prophylaxis is taught in lines 7 and 8, column 14. However, prophylaxis against basal cell carcinoma is nowhere taught in the reference. Thus, the anticipation rejection against claim 50 is withdrawn.

Information Disclosure Statement

3. The copy of PTO-1449 and the post card receipt supplied by Applicants is acknowledged. The Examiner cannot find any references in the file and a search has been started.

Claim Objections

4. Objection remains to claims 2-4 under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The four claims concern the B polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride. There Applicants state that only two polymorphs are known, A and B. There are only two purity limitations in the four objected claims, "substantially homogeneous" in claim 1 and "substantially free of the A polymorph" in claim 3. A substance, which exhibits x-ray diffraction peaks, must be crystalline. The Examiner can see no difference in

these limitations. Thus, all four claims are to the same substance with the same purity limitation.

5. Objection remains to claims 6 and 7 under 37 CFR 1.75 as being a substantial duplicate of claim 5, for reasons cited previously.

6. Objection is made to claims 56 and 57 under 37 CFR 1.75 as being a substantial duplicate of claim 55, for reasons cited above.

7. Objection is made to claim 58 under 37 CFR 1.75 as being a substantial duplicate of claim 5. It is not logical that a composition intended for therapy, as is claim 5, would not contain a therapeutically effective amount of the compound of claim 1.

8. Objection is made to claim 62 under 37 CFR 1.75 as being a substantial duplicate of claim 5. Applicants have chosen a different and ultimately equivalent way of expressing the X-ray data. Both are compositions of the identical substance.

Applicants argue that claim 3 differs from claim 1 because "substantially homogeneous" is not necessarily "substantially free of the A polymorph". This is not persuasive. Neither phrase is defined in the specification and any homogenous substance must be free of other substances. Applicants made no argument concerning the objection to claims 2, 4, and 6.

Claim Rejections - 35 USC § 112

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 14 and 17-22 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants are not enabled for treatment of "abnormal cell growth" generally. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

Applicants argue that claim 14 is drawn to the treatment of specific cancers. They also point to the clinical data presented on the pages spanning 50-53 as enabling their claim. This is not persuasive. Lines 29-30, page 23 says among other diseases that "tumor cells (tumors) both benign and malignant, expressing an activated Ras oncogene" are to be treated. Thus, Applicants' claim is not limited to the specific tumors of claim 17.

10. Claim 50 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention. Applicants are not enabled for preventing basal or squamous cell carcinoma. The only established prophylactics are vaccines not the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine salt such as present here. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of proliferative diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Applicants have replaced "chemoprevention" with "prophylaxis against". The Examiner can see no difference in meaning.

11. Claim 63 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Is this claim restricted to cancer therapy? Are there additional reasons for "inducing differentiation of tumor cells"? Clarification is requested.

12. Claim 63 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific tumors, does not reasonably provide enablement for cancer treatment generally or for other uses of tumor cell differentiation which are not therapeutic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The issue of general tumor treatment is discussed above. Beyond the passage in lines 29-31, page 13 Applicants provide no explanation of why one would want to do this.

Claim Rejections - 35 USC § 102

13. Claims 1-7, 14-23, and 52-54 remain rejected under 35 U.S.C. 102(e) as being anticipated by Schnur ('498). The reference teaches the synthesis and crystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride in Example 20, lines 30-49, column 22. Applicants have amply characterized their material, polymorph B but there is no side-by-side comparison to the material taught by the reference. Applicants state in lines 15-19, page 16 the material made by Schnur ('498) is a mixture of polymorph A and polymorph B. There is no data provided in the specification as to the ratio A and B in the prior art. Could the material prepared by Schnur ('498) contain substantial

amounts of polymorph B? Could it be as high as 70%? Might it be 90%? Applicants provide no data as to the numeric ratio of A to B in their material. Line 2, page 5 says that it is "substantially homogeneous" polymorph B. What does this mean? Must it be 99.9% polymorph B? Could it be 90%? Could it be 51%?

Treatment of lung, ovarian, head, neck, colorectal, and renal cancer is taught in lines 8-11, column 14 of the reference.

Applicants make two arguments, firstly, that Schnur ('498) does not use the word polymorph. Secondly, that Applicants' process used to produce the crystal form of claim 1 differs from that of the reference used to produce their crystalline material. Neither argument is persuasive. Applicants' claim 1 is for a specific crystal form of a known compound salt. Patentability of Applicants' crystal form derives from the structure of that crystal, specifically the internal arrangement of the molecule within the crystal lattice and the form of the crystal lattice itself. *In re Spada* 15 USPQ2d 1655 (new property of previously known composition does not impart patentability to the composition). The relevance to patentability of the x-ray characteristics exhibited by Applicants' compound is limited to assessing the significance of their crystal structure over the prior art. When the Examiner shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re King* 231

USPQ 136; *In re Ludtke* 169 USPQ 563. The inherency case of anticipation can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best* 195 USPQ 430 (prior art zeolite with same $SiO_2/Al_2O_3$and Na_2O/Al_2O_3 molar ratios but not specifically disclosing x-ray powder data either anticipates based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively).

Secondly, the patentability of a new chemical structure is independent of how it is made, *In re Hoeksema* 141 USPQ 733 (product patentable even though the process was obvious).

14. Claims 55-60 are rejected under 35 U.S.C. 102(e) as being anticipated by Schnur ('498). Compositions are taught in the reference in the passage spanning line 63, column 15 to line 45, column 16. Tablets are specifically mention in line 64. Applicants admit that polymorph B is taught by the reference. The silence of the reference as to the amount of polymorph B present does not make Applicants claims patentable for the reasons cited above.

15. Claims 62-68 are rejected under 35 U.S.C. 102(e) as being anticipated by Schnur ('498). Applicants admit that the prior art material and the composition made from it contain polymorph B. The prior art and Applicants' silence as to the ratios do not make their claims patentable for reasons cited above. Cancer therapy

broadly in found in claim 28 of the reference. Applicants' claim 64 is an independent claim with no limitation as to crystal form. Treatment of lung cancer, leukemia, and cervical tumors is taught in lines 6-16, column 14. treatment of "immunological disorders" is taught in 28, column 14. treatment t of skin cancer is taught in claim 29. The concept of additional anti-tumor agents is taught in lines 46-51, column 16.

Claim Rejections - 35 USC § 103

16. Claims 24-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Schnur ('498). The reference teaches crystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride from chloroform and ether. The Applicants claim crystallization from water and alcohol. The difference between the claimed and taught processes is the solvent employed. Changes in solvent are a matter of routine experimentation to the process chemist trying safer and less flammable solvents for the pilot plant. No more than routine skill is required for the process chemist to optimize the solvent choice. To quote the Board of Patent Appeals and Interferences *Ex parte Goldschmidt*, 123 USPQ 41 "It is our opinion that it does not amount to invention for the skilled chemist ... to determine ... which specific organic solvent is most suitable".

Applicants make two arguments. Firstly, that they were not told where in the reference to find the teaching of solvent. Secondly, that the prior art reference made no suggestion to change solvent or which other solvent to choose. The solvent teaching is in lines 45-48, column 22. The Examiner pointed to this

passage in the anticipation rejection, using the same reference, in point #9 of the previous office action .

Secondly, the Examiner did not use the primary reference for a suggestion to change solvent. The economic and safety motivation was suggested above. In addition, routine experimentation does not require a specific teaching. Of course, if Applicants' can establish to novelty of their crystal form, then their process would be non-obvious, *In re Ochiai* 37 USPQ2d 1127.

Allowable Subject Matter

17. Claim 61 is allowed. The prior art does not suggest any clarifying step in their process.

18. Claim 69-72 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: The prior art does not teach treatment using the specific additional antibodies, MMP inhibitors, or radiation treatment required by these claims.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-

MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
August 28, 2002